

**UNITED STATES AIR FORCE
RESEARCH LABORATORY**

**EFFECT OF JP-8 VEHICLE ON
DERMAL PENETRATION OF
HYDROCARBON COMPONENTS FROM
JET FUEL**

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March 2000

Interim Report - March 1999 - April 2000

20060630295

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TECHNICAL REVIEW AND APPROVAL

AFRL-HE-WP-TR-2000-0045

This report has been reviewed by the Office of Public Affairs (PA) and is releasable to the National Technical Information Service (NTIS). At NTIS, it will be available to the general public, including foreign nations.

This technical report has been reviewed and is approved for publication.

FOR THE DIRECTOR



DAVID R. MATTIE, PH.D
Acting Branch Chief, Operational Toxicology Branch
Air Force Research Laboratory

REPORT DOCUMENTATION PAGE			Form Approved OMB No. 0704-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503.				
1. AGENCY USE ONLY (Leave blank)		2. REPORT DATE March 2000		3. REPORT TYPE AND DATES COVERED Interim Report - March 1999 - April 2000
4. TITLE AND SUBTITLE Effect of JP-8 Vehicle on Dermal Penetration of Hydrocarbon Components From Jet Fuel			5. FUNDING NUMBERS Contract F41624-96-C-9010 PE 61101F PR 2312 TA 2312A WU 2312A204	
6. AUTHOR(S) Robinson, P., McDougal, J.				
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) ManTech-Geo Center Joint Venture PO Box 31009 Dayton, OH 45437-0009			8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES) Human Effectiveness Directorate Air Force Research Laboratory Wright-Patterson AFB, OH 45433-7400			10. SPONSORING/MONITORING AGENCY REPORT NUMBER AFRL-HE-WP-TR-2000-0045	
11. SUPPLEMENTARY NOTES				
12a. DISTRIBUTION AVAILABILITY STATEMENT Approved for public release; distribution is unlimited.			12b. DISTRIBUTION CODE	
13. ABSTRACT (Maximum 200 words) Published data on the dermal penetration of hydrocarbon components from the widely used jet fuel JP-8 are analyzed. The log of the dermal penetration coefficient Kp was observed to have a linear dependence on lipophilicity as estimated from the log-octanol-water partition coefficient Ko/w (with slight dependence on molecular weight). This semi-empirical relation can be used to predict (estimate) Kp values for other JP-8 components. In contrast to the penetration of compounds from aqueous vehicle, the more lipophilic compounds penetrated the skin at a lower rate, consistent with results on the partitioning of compounds into the stratum corneum from different vehicles.				
14. SUBJECT TERMS JP-8 Hydrocarbon			15. NUMBER OF PAGES 22	
			16. PRICE CODE	
17. SECURITY CLASSIFICATION OF REPORT UNCLASSIFIED	18. SECURITY CLASSIFICATION OF THIS PAGE UNCLASSIFIED	19. SECURITY CLASSIFICATION OF ABSTRACT UNCLASSIFIED	20. LIMITATION OF ABSTRACT UL	

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Preface

This research was accomplished at the Operational Toxicology Branch, Human Effectiveness Directorate of the Air Force Research Laboratory.

Some of this work was presented as a poster at the 39th Annual Meeting of the Society of Toxicology, Philadelphia, March 2000.

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Abstract

Published data on the dermal penetration of hydrocarbon components from the widely used jet fuel JP-8 are analyzed. The log of the dermal penetration coefficient K_p was observed to have a linear dependence on lipophilicity as estimated from the log-octanol-water partition coefficient K_o/w (with slight dependence on molecular weight). This semi-empirical relation can be used to predict (estimate) K_p values for other JP-8 components. In contrast to the penetration of compounds from aqueous vehicle, the more lipophilic compounds penetrated the skin at a lower rate, consistent with results on the partitioning of compounds into the stratum corneum from different vehicles.

Introduction

JP-8 is a kerosene based fuel consisting of a complex mixture of hundreds of components from a number of hydrocarbon classes, including straight chain alkanes, branched chain alkanes, cycloalkanes, diaromatics and naphthalenes. Human exposures to JP-8 in the vapor, aerosol and liquid forms all have the potential to be harmful. Situations where fuel becomes aerosolized have the greatest potential to be a hazard via inhalation. Both aerosol and liquid forms of JP-8 have the potential to cause local and systemic effects with prolonged or repeated skin contact. JP-8 aerosol has been shown to result from aircraft engine starts at low ambient temperatures. This aerosol, from incomplete combustion, may be inhaled, irritate the eyes or soak clothing and come into prolonged contact with the skin of ground personnel. Other potential dermal exposures to JP-8 are: 1) splashes during refueling or fuel handling, 2) handling engine parts which are coated with fuel, 3) coming in contact with sides of fuel tank during fuel tank maintenance operations, or 4) coming in contact with fuel leaks on the underside of the aircraft or on the ramp.

EPA has recently issued draft guidelines for the conduct of health risk assessments of chemical mixtures (EPA, 1999). These guidelines stress that evaluation of risk posed by exposure to multiple chemicals can only come about with a solid understanding of the toxicity of chemical agents and the factors that control their absorption, metabolism, distribution and elimination. The present paper considers the dermal absorption of individual hydrocarbon components from JP-8. Strictly speaking, the penetration of each component is affected by its interactions with all the other components in the mixture. The key simplifying assumption that makes this problem tractable is to consider that each component is affected by a composite vehicle consisting of the remaining hydrocarbon fractions, and because of the large number of components (each contributing relatively little to the total composition), that this vehicle can be considered essentially the same for all components.

The current study analyzes previously published data on the penetration of JP-8 into and through clipped, dermatomed rat skin in vitro (McDougal et al., in press). In that study, static diffusion cells were used to measure the flux of JP-8 and its major components across rat skin and the kinetics of absorption into the skin. Thirteen individual components penetrated into the receptor solution in sufficient quantities to be measured by GC/FID and allow the calculation of a steady-state flux and penetration coefficient K_p (flux divided by applied concentration).

The Data

Table 1 gives calculated dermal penetration coefficients Kp (cm/hr) for those components of JP-8 that were measured in the receptor solution, together with relevant physico-chemical properties (octanol-water partition coefficient, Ko/w, and molecular weight, MW).

TABLE 1.

Chemical characteristics and log of the measured permeability coefficients (Kp) for each of the chemical components identified in the receptor solutions from JP-8 exposures. (From McDougal et al., in press). Note that the more negative the log Kp value, the slower the rate of penetration through the skin.

Component	Molecular Weight	Log K _{ow}	Log Kp (cm/hr)
Diethylene glycol monomethyl ether	120.2	-0.68	-1.09691
Methyl benzene (toluene)	92.1	2.69	-2.95861
Naphthalene	128.2	3.37	-3.29243
Ethyl benzene	106.2	3.13	-3.50864
Dimethyl benzene (xylene)	106.2	3.18	-3.76955
Methyl naphthalenes	142.2	3.87	-3.79588
Trimethyl benzene	120.2	3.58	-3.88606
Dimethyl naphthalenes	156.2	4.38	-4.03152
Decane	142.3	6.25	-4.25964
Nonane	128.3	5.65	-4.37675
Undecane	156.3	6.94	-4.60206
Tridecane	185.4	7.57	-4.82391
Dodecane	170.3	7.24	-4.85387

These penetration coefficients are characteristically dependent on the molecular weights and particularly on the octanol/water partition coefficients of the compounds as shown in Figure 1. Note that the more lipophilic the compound (i.e. the larger log Ko/w), the *lower* the Kp value.

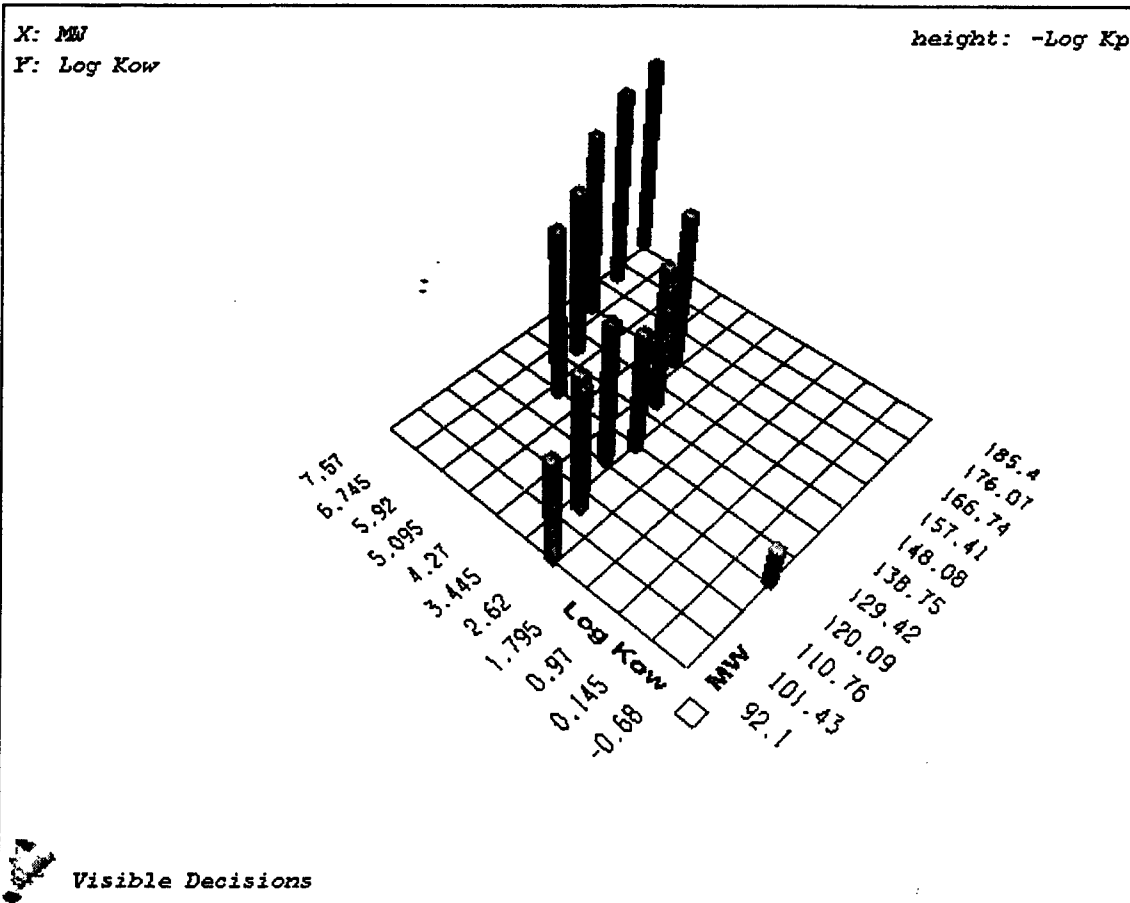


Figure 1. 3-D plot of the negative of the log of the dermal penetration coefficient ($-\log K_p$) versus the molecular weight (MW) and octanol water partition coefficient ($\log K_o/w$) for the 13 components of JP-8 measured in the receptor solution. Note that in this plot, the larger the height of the columns, the slower the chemical penetrates the skin. The upper cluster of chemicals are aliphatics, the lower cluster are aromatics, while the outlier is diethyl glycol monomethyl ether (DIEGME).

Table 2 gives the concentrations of JP-8 components in the skin itself at the end of the 3.5 h exposures, together with the ratio relative to concentrations in JP-8 (McDougal et al., in press). The mass in the skin increases roughly with concentration in JP-8 itself. In addition, the mass ratio skin/JP-8 decreases with increasing lipophilicity (as estimated by the octanol-water partition coefficient) (see Figure 2), consistent with decreasing partitioning into the stratum corneum, the likely major repository for such lipophilic materials in the skin. It should be noted, however, that the skin here includes the viable epidermis and a significant portion of the dermis, which would also provide less congenial environments for the more lipophilic materials, and thus contribute to this trend.

TABLE 2
Concentrations of JP-8 components that were found in the skin at the end of the 3.5-hour exposures in static diffusion cells compared to the concentration of that component in JP-8.

Component	Mass in Skin (mg/g) \pm S.D.	Conc. in JP-8 (mg/ml)	Log Kow	Ratio (ml/g times 10^{-3})
Nonane	0.077 \pm 0.018	9.2	5.65	8.4
Decane	0.196 \pm 0.047	30.2	6.25	6.4
Undecane	0.266 \pm 0.070	48.3	6.94	5.5
Dodecane	0.143 \pm 0.041	36.1	7.24	4.0
Tridecane	0.092 \pm 0.035	21.9	7.57	4.2
Tetradecane	0.055 \pm 0.022	14.6	7.9 (est)	3.8

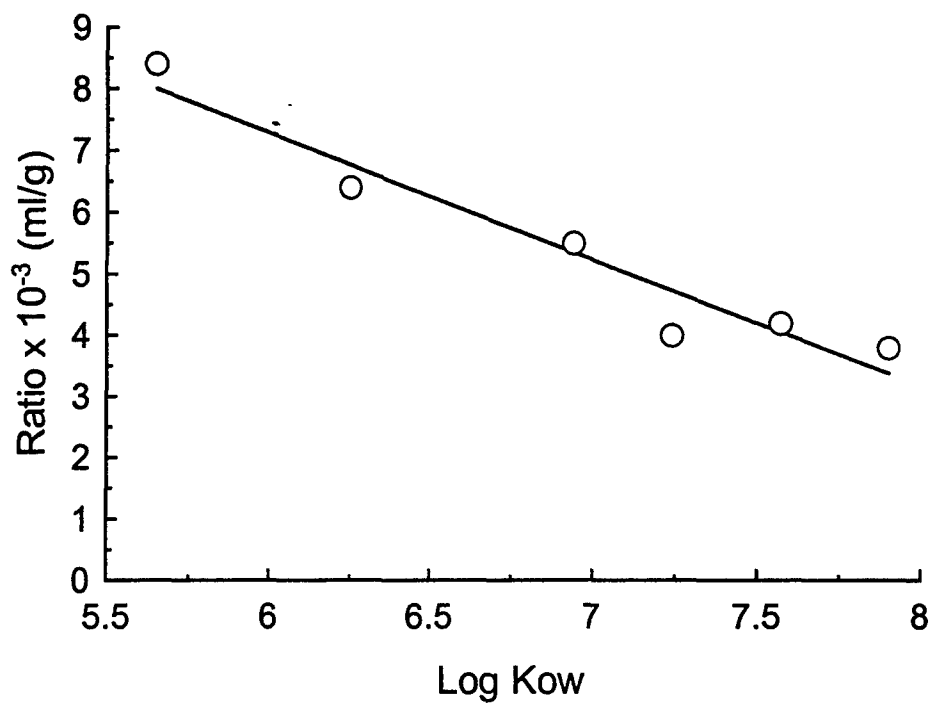


Figure 2. Linear regression of the ratio in skin/JP-8 (ml/g x 10⁻³) from Table 2 versus log Kow. The line is given by $\text{Ratio} = 19.6 - 2.05 \times \log Kow$, $r^2 = 0.93$.

Analysis

Analysis of the log K_p data by multiple linear regression against log K_{o/w} and MW (SigmaStat™, Jandel Scientific) gave the following equation (see Appendix for details):

$$\log K_p = -2.69 - 0.471 \log K_{o/w} + 0.00716 MW \quad \dots(1)$$

where K_p is the permeability coefficient, K_{o/w} is the octanol/water partition coefficient and MW is the molecular weight. The correlation coefficient (R²) for this relationship is 0.898, which is higher than most of the published correlation approaches. However, it appears that only log K_{o/w} was in fact necessary to account for the variability in log K_p (the molecular weights for the compounds covered the limited range from 92 to 170). Linear regression of log K_p against log K_{o/w} gives:

$$\log K_p = -1.99 - 0.408 \log K_{o/w} \quad \dots(2)$$

with R² = 0.898 (see Figure 3).

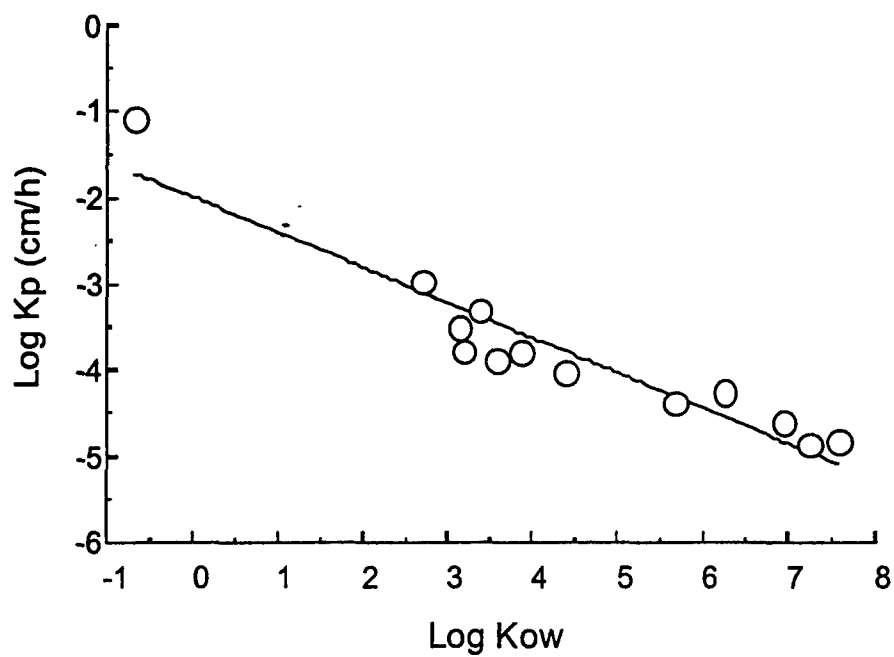


Figure 3. Linear regression of $\log K_p$ (cm/h) against $\log K_o/w$ for 13 components of JP-8 measured in the receptor solution. The equation of the line is given by Eq. (2) in the text

Discussion

Several correlation approaches for estimating permeability coefficients for chemicals in water vehicle are found in the literature (see Bunge and McDougal, 1998). These approaches are based on molecular weight and the octanol/water partition coefficient as predictors of penetration. Application of this approach for hydrocarbon components in JP-8 gave equation (1) and (2) above. This is illustrated in Figure 3. This same relationship (without the data points) is also shown as the lower line of Figure 4. These relationships can be used to predict penetration of other (similar) components of JP-8 that were not able to be measured, based solely on their physico-chemical properties. Note that the log octanol/water partition coefficient has a much larger impact on the permeability than the molecular weight, due at least in part to the limited range of molecular weights of the compounds studied.

In contrast to our study, correlations from studies in which water was the vehicle show a positive impact of K_o/w and a negative impact of the molecular weight on the permeability coefficient (Flynn, 1990; Potts & Guy, 1992; Robinson, 1996) (see Figure 4, upper curve). The difference is in the vehicle. JP-8 is more lipid-like than the skin and as the octanol/water partition coefficient goes up (larger K_o/w) the chemical would have a tendency to stay in the lipid vehicle. In the aqueous situation, when the octanol/water partition coefficient goes up, the tendency for the chemical to move into the lipophilic skin (and hence skin penetration) is enhanced. Thus the two curves in Figure 4 thus have opposite slopes.

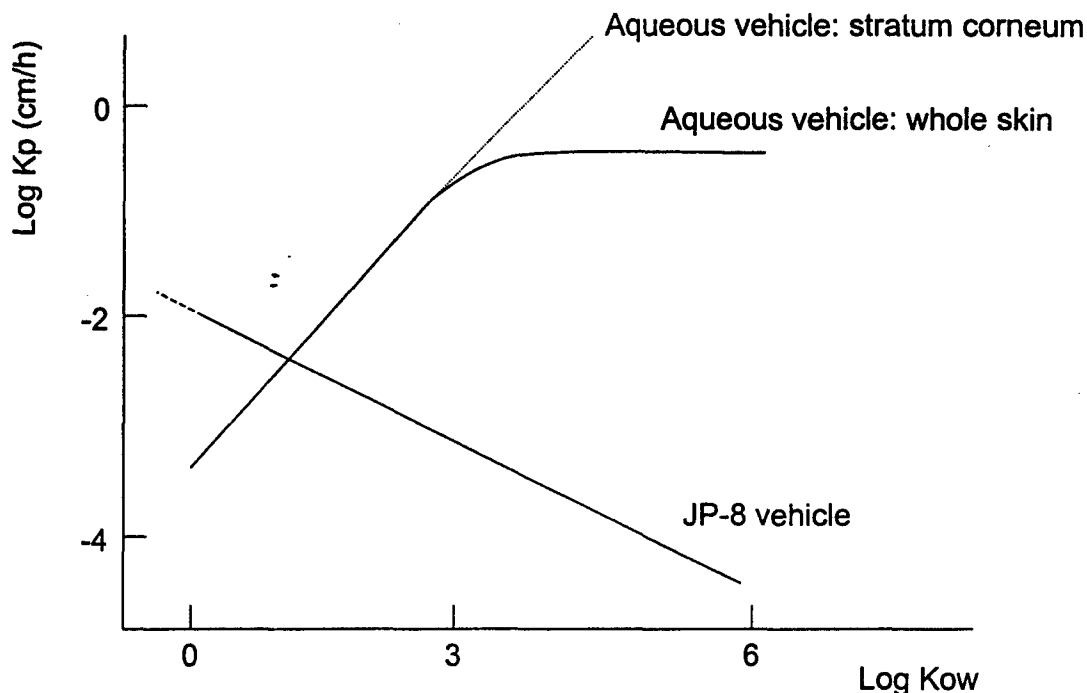


Figure 4. Representation of the dependence of dermal penetration K_p on log octanol-water partition coefficient (K_o/w) from aqueous and JP-8 vehicles. The curves for aqueous vehicle are adapted from the semi-empirical relationships derived by Potts & Guy, 1992 and Wilschut et al., 1995; the JP-8 vehicle line is from Figure 3.

This general trend of decreased dermal absorption with increased lipophilicity is also seen in the concentrations of JP-8 components in the skin itself as measured by the ratio of concentrations in skin versus JP-8 itself (Table 2). This trend has been observed before, most notably by Scheuplein (1965, 1980), who calculated stratum corneum:vehicle partition coefficients (K_{mv}) for alcohols of varying chain lengths from a number of different vehicles (Figure 5), and found these to be in good agreement with measured permeability coefficients. Increased chain length corresponds to increased lipophilicity.

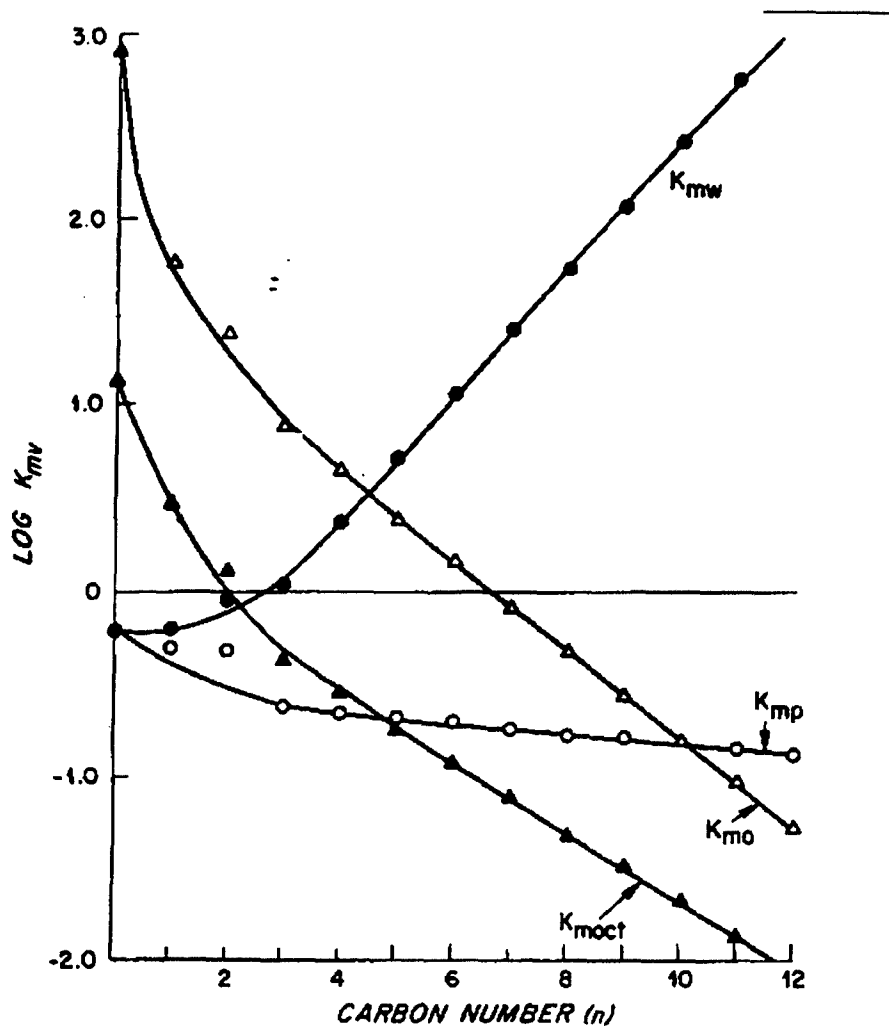


Figure 5. Effect of vehicle on the stratum corneum: vehicle partition coefficient, K_{mv} (theoretical); from Scheuplein, 1980. Here "oct" represents octanol vehicle, "o" represents oil, "p" (sic) represents butanol, and "w" represents water vehicle. Each vehicle would increase penetration for those solute-vehicle combinations above the horizontal line, and would inhibit it for those below.

Note that this "reverse partitioning" effect of the lipophilic vehicle applies not just to lipophilic materials, but the hydrophilic DIEGME as well ($\log K_{o/w} = -0.68$) (Figure 3). In this case, penetration from JP-8 vehicle is enhanced relative to aqueous vehicle, illustrated by the cross-over of the two curves on the left hand side of Figure 4. Note that the two curves cross at $\log K_{o/w} \sim 1$, corresponding, for example, to the octanol-water partitioning of pentanol ($K_{o/w} \sim 1.5$). This suggests that the permeability of pentanol would be nearly the same from water or JP-8. Scheuplein (1980) observed a similar intersection of stratum corneum/water (K_{mw}) and stratum corneum/oil partition coefficients (K_{mo}) (the latter representing a lipophilic vehicle) near the 5 carbon number alcohol, pentanol (Figure 5).

Consideration of Figure 4 for aqueous and JP-8 vehicle lead to speculations as to the generalized effect of vehicles of different lipophilicities on dermal penetration. One can envisage a series of curves for different vehicles of different lipophilicities, intersecting in the same general area as the two curves illustrated in Figure 4 (where the penetrating compounds are neither hydrophilic nor particularly lipophilic, and thus largely unaffected by the lipophilicity of the vehicle). Such characteristics need to be explored experimentally before more general predictive tools can be developed. A possible generalization of the compound/vehicle dichotomy is to neat materials, in which the compound can be considered as its own vehicle.

As in any in vitro dermal penetration study, the effect of the receptor solution on permeability measurement needs to be considered, particularly for such lipophilic materials as the JP-8 components considered here (see Robinson, 1996 for a general discussion of this issue). Ultimately, we would wish our in vitro studies to simulate as closely as possible the in vivo situation in which the capillary network of the skin efficiently clears absorbed material into the systemic circulation. While modifications to the receptor solution can be made to facilitate the removal of lipophilic materials from the skin in vitro, this

invariably involves compromises, and it is not clear to what extent the penetration characteristics in vitro actually represent those in vivo. As a result, this in vitro data should be replicated in vivo.

References

- EPA/NCEA *Guidance for Conducting Health Risk Assessment of Chemical Mixtures* (April, 1999, NCEA-C-0148) 1999.
- Flynn, G.L. Physicochemical determinants of skin absorption. In *Principles of route to Route Extrapolation for Risk Assessment*, T.R. Gerity & C.J. Henry, eds. Elsevier Science Publishing Co, Inc., 1990.
- Kasting, G.B. & Robinson, P.J.: Can we assign an upper limit to skin permeability? *Pharm. Res.* 10: 930-931, 1993.
- McDougal, James N., Daniel L. Pollard, Wade Weisman, Carol M. Garrett, and Thomas E. Miller. Assessment of Skin Absorption and Penetration of JP-8 Jet Fuel and its Components. *Toxicological Sciences* 55, xxx-xxx, 2000
- Potts, R.O. and Guy, R.H. Predicting skin permeability. *Pharm Res* 9, 663-669, 1992
- Robinson, P. A Predictive Model For Dermal Penetration. In *Alternatives to Animal Testing*, S. Lisansky, R. Macmillan & J. Dupuis, eds. CPL Press, Newbury, U.K., 1996, pp 344-345.
- Robinson, P. Pharmacokinetic modeling of JP-8 jet fuel components. I. Nonane and C9 -C12 aliphatic components. AFRL/HEST Technical Report, December 1999.
- Scheuplein, R.J. *J Invest Derm* 45, 334-346, 1965.
- Scheuplein, R.J. Percutaneous absorption: theoretical aspects. In P. Mauvais-Jarvis, C.F.H. Vickers & J. Wepierre, eds. *Percutaneous Absorption of Steroids*, Academic Press, London, 1980.
- Wilschut, A., ten Berge, W.F., Robinson, P.J. & McKone, T.E.: Estimating skin permeation: the validation of five mathematical skin permeation models. *Chemosphere*, 30: 1275-1296, 1995.

Appendix: Multiple linear regression

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Multiple Linear Regression

$$\log Kp = -2.69 - (0.471 * \log Kow) + (0.00716 * MW)$$

N = 13.0

R= 0.957 Rsqr= 0.915 Adj Rsqr= 0.898

Standard Error of Estimate = 0.3162

	Coefficient	Std. Error	t
Constant	-2.68513	0.52179	-5.15
log Kow	-0.47077	0.05916	-7.96
MW	0.00716	0.00502	1.43

	P	VIF
Constant	0.0004	
log Kow	<0.0001	2.22
MW	0.1837	2.22

Analysis of Variance:

	DF	SS	MS
Regression	2	10.764	5.3820
Residual	10	1.000	0.1000
Total	12	11.764	0.9803

	F	P
Regression	53.8	<0.0001
Residual		
Total		

Column	SSIncr	SSMarg
Constant	10.560	6.330
log Kow	0.204	0.204
MW		

The dependent variable log Kp can be predicted from a linear combination of the independent variables:

	P
log Kow	<0.0001
MW	0.1837

Not all of the independent variables selected appear necessary. The following variables appear to account for the ability to predict log Kp: log Kow

Normality Test: Passed (P = 0.4079)

Homoscedasticity Test: Passed (P = 0.1790)

Power of performed test with alpha = 0.0500: 1.0000